UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,268	07/21/2000	STEPHEN D. GILLES	LEX-007	3473

21323 7590 03/21/2003

TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 03/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/621,268	Gilles et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above, claim(s) *27-43* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-26 and 44-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *7/21/00* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to this application has been changed.

2. Claims 1, 2, 15, 18 and 26 have been amended. Claim 46 has been added. Claims 27-43 remain withdrawn from consideration. Claims 1-26 and 44-46 are under consideration.

3. After review and reconsideration the Office action of Paper No. 8 is vacated.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

5. Claims 10, 17 and 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 10 and 22 recite the specific embodiments of prostate-specific membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor-specific protein which are the specific embodiments of claims 1 and 15 on which claims 10 and 22 depend therefrom. Claim 22 recites the specific embodiment of "linked by a polypeptide bond to an immunoglobulin heavy chain constant region" which is also recited as a specific embodiment of claim 15, clause b, therefore claim 17 fails to further define claim 15.

6. Claims 8-10, 15-26, and 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "preselected" in claim 10 lacks antecedent basis in claim 1. The recitation of "preselected" in claims 17 and 22 lacks antecedent basis in claim 15. Further, it is unclear how "preselected" describes or limits "antigen" and it is not possible to discern the difference between a "preselected antigen" and an antigen in claims 10, 17, 22, 44 and 45 given

the teachings of the specification. For purpose of examination the claims will be read as being drawn to any antigen.

Claim 8 recites: heavy chain constant region is defined by an amino acid sequence corresponding to an amino acid sequence defining an immunoglobulin heavy chan constant region present in the same species as the mammal. Claim 9 recites: wherein the amino acid sequence defining the immunoglobulin heavy chain constant region corresponds to a human immunoglobulin heavy chain constant region. Claim 26 recites: heavy chain constant region is defined by a amino acid sequence corresponding to an amino acid sequence defining a human immunoglobulin heavy chain constant region. It is unclear how "corresponding to an amino acid sequence defining a human immunoglobulin heavy chain constant region" defines the claimed heavy chain constant region because it is unclear what alterations and deviations from human heavy chain constant region are encompassed by "corresponding to an amino acid sequence" and "defining a human immunoglobulin heavy chain constant region" as there are no precise definitions in the specification for what is encompassed by the term "corresponding to an animo acid sequence" or "defined by an amino acid sequence". Amendment of claims 4 to read --- wherein the immunoglobulin heavy chain constant region is an immunoglobulin heavy chain constant region present in said mammal--- and amendment of claim 26 to read ---wherein the immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region--- will obviate this rejection.

Claim 15 is vague and indefinite in the recitation of "comprising an admixture for intramuscular, intravenous, transdermal or subcutaneous administration" without a recitation of a specific ingredient or physical property incorporated into clause a or b that would render patentable distinctness to the claimed admixture from any other admixture having the specific embodiments of either clause a or clause b.

Claim 46 recites "the method consisting essentially of". The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those

that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). "A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising.".

Claims 1, 10, 15 and 22 are vague an indefinite by reference to "a prostate specific membrane protein". It is unclear if the claims are limited to the Prostate Specific Membrane Antigen as disclosed by Israeli et al (U.S. 5,538,866) or if "a prostate specific membrane antigen" encompasses other membrane antigens in the prostate in addition to the aforesaid. For purpose of examination, both alternatives will be considered.

7. Claims 1-26 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

Claims 44 and 45 are drawn in part to a method for enhancing the immunogenicity of an antigen in a mammal, the method comprising administering to a mammal fusion proteins comprising localizing proteins. Localizing proteins comprising a large genus of proteins including any protein, antibody or fragment thereof which binds to a specific receptor on a specific organ or

cell type. Localizing protein can also include oligomer peptides for localization to the nucleus or cytoplasm. The disclosure and the claims as filed set forth only the Fc fragment of the immunoglobulin constant region as a protein which would be selectively taken up by antigen presenting cells. Neither the specification or claims as filed contemplated the "localizing protein" which is much broader in scope that the immunoglobulin heavy chain constant region. One of skill in the art would conclude that applicant was not in possession of "localizing protein" at the time the application was filed.

(B)As drawn to written description

The claims are drawn to compositions comprising antigen and adjuvant fusion proteins and methods of using said compositions, wherein the antigen is an ectodomain of a cytokine receptor, a viral protein and a tumor specific protein. Thus the composition claims encompass three distinct genuses of proteins: 1. ectodomains of cytokine receptors, 2. viral proteins and 3. tumor specific proteins and the method claims rely on said genuses. The claims are also drawn to compositions comprising "a prostate specific membrane antigen" and methods relying thereupon and for the reasons set forth in the rejection under 112, second paragraph above, are also drawn to a genus of proteins expressed in or on the prostate cellular membrane. In addition, for the reasons set forth in the 112, second rejection above, claims 8, 9 and 26 also encompass a genus of immunoglobulin constant regions. Thus the scope of the claims includes numerous structural variants as fusion proteins within each genus and the genus is highly variant because there is no limit on the structural variation that is encompassed within each genus. The specification does not disclose structural attributes for "a prostate specific membrane antigen" which would determine if a given protein belonged to the claimed genus. Further, the specification does not define "a prostate specific membrane antigen" by means of a prior art reference, wherein the genus of proteins would be limited to a single amino acid sequence. One of skill in the art would reasonably conclude that applicant was not in possession of the broadly claimed genus of proteins relied upon in the instant method and composition claims.

8. Claims 15 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a dimeric antigen fusion protein or a dimeric adjuvant fusion protein, wherein said dimeric protein is made by disulfide bonds, does not reasonably provide enablement for an antigen or adjuvant fusion protein linked by a disulfide bond to a second immunoglobulin heavy chain constant region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ (CCPA 1977)). Additionally the courts have determined that "...where a statement is , on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factor are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: Claim 26 is drawn to antigen or adjuvant fusion protein linked by a disulfide bond to a second immunoglobulin heavy chain constant region. When given the broadest reasonable interpretation the claim reads on an antigen or adjuvant fusion protein, wherein said fusion proteins comprise an immunoglobulin heavy chain region, fused to a immunoglobulin heavy chain region that is not part of a fusion protein. In addition, said non-fused constant region can be an immunoglobulin constant region which differs from the constant region of the fusion protein.

The state of the prior art and the predictability or lack thereof in the art:

The art teaches that the immunoglobulin constant region of an antibody or a fusion protein interacts with antigen presenting cells expressing the Fc receptor, allowing the uptake of said antibody or antibody complexed with antigen into said antigen presenting cell (Guyre et al, Cancer Immunol Immunother 1997, Vol. 45, pp. 146-148, reference C1 of the I.D.S. filed October 10, 2001). The art teaches that directing of an antigen to the Fc receptor increases the effectiveness of immunization by said antigen (Heijnen et al, Journal of Clinical Investigation, 1996, Vol. 97, pp. 331-338). Thus the art teaches that the Fc receptor acts as a means of delivering antigen or fusion protein to immune cells. The art also teaches that antibodies comprise dimers of the heavy chain constant region linked by disulfide bonds.

The amount of direction or guidance presence and the presence or absence or working examples:

The specification teaches the dimerization of antigen and/or adjuvant fusion proteins by means of linking the Fc receptor by disulfide bonds as exemplified by figures 1C through 1G.

The breath of the claims and the quantity of experimentation needed:

When given the broadest reasonable interpretation, the claims encompass an antigen and/or adjuvant fusion protein, wherein said fusion protein comprises the heavy chain constant region, linked to a molecule which consists only of an immunoglobulin heavy chain constant region. The specification does not teach an auxiliary use for this protein as only one molecule of antigen and/or adjuvant will be delivered by binding of the composition to the Fc receptor of an

antigen presenting cell versus the delivery of two molecules of antigen and/or adjuvant that would be bound in the case of the molecules of figures 1C through 1G. There is no teachings in the specification of how to use said molecule containing two immunoglobulin constant regions but only one antigen and/or adjuvant proteins. One of skill in the art would be subject to undue experimentation in order to find a use for the broadly claimed molecule.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claim 46 is rejected under 35 U.S.C. 102(b) as being anticipated by Heijnen et al (Journal of Clinical Investigation, 1996, Vol. 97, pp. 331-338). Claim 46 is drawn to a method for enhancing the immunogenicity of an antigen in a mammal comprising administering to the mammal intramuscularly, intravenously, transdermally or subcutaneously, a fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to the

antigen thereby to elicit an immune response against the antigen, wherein the antigen of the fusion protein elicits a stronger immune response in the mammal than the antigen alone.

Heijnen et al disclose a method of enhancing the immunogenicity of an antigen comprising the subcutaneous administration of a fusion protein comprising the variable chains of an antibody directed against human Fcgamma I receptor, H22, fused to a humanized immunoglobulin constant region (page 336, under the heading "Antibody responses to hFcgammaRI-targeted antigens in transgenic mice", page 332, first column, under the heading "Antibodies", and second column, under the heading "Immunizations and ELISA"). Heijnen et al disclose that a control antibody, SB82, which did not bind to the Fcgamma I receptor, but contained the same humanized constant region, induced an IgG1 antibody response in only three of the eight mice which were immunized, which is in contrast to the mice administered the H22 antibody which developed high levels of H22 specific IgG1 and significant levels of H22-specific IgG2a and 2b. Heijen et al concludes that "targeting of antigen to hFcgammaRI expressed on myeloid cells triggers enhanced antigen-specific antibody responses in vivo". As the H22 antibody triggered an enhanced immune response relative to the SB82 antibody which was serving an untargeted antigen, the specific embodiment of eliciting a stronger immune response relative to the antigen alone, is also fulfilled.

11. Claims 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Blumberg et al (U.S. 6,086,875, reference A7 of the IDS filed October 10, 2001). Claim 15 is drawn to a composition for eliciting an immune response against an antigen in a mammal comprising as admixture for intramuscular, intravenous, transdermal or subcutaneous administration selected from the group consisting of (a) an antigen fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to the antigen admixed with an adjuvant wherein the antigen is selected from the group consisting of prostate-membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor-specific protein; and (b) an antigen fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide

bond to the antigen wherein the antigen is selected from the group consisting of prostate-membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor-specific protein, admixed with an adjuvant fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to an adjuvant protein. Claim 16 is drawn to the composition of claim 15, wherein the adjuvant of clause (a) comprises a fusion protein comprising an immunoglobulin constant region linked b a polypeptide bond to an adjuvant protein. Claim 17 embodies the composition of claim 15 wherein the antigen of clause (b) is linked by a polypeptide bond to an immunoglobulin heavy chain constant region. It is noted that the metes and bonds of claim 15 cannot be determined as regards the "admixture for intravenous, intramuscular , transdermal or subcutaneous administration" for the reasons set forth in the rejection under 112, second paragraph, above.

Blumberg et al teach a composition for eliciting an immune response against an antigen in a mammal comprising the administration of antigens coupled to molecules that bind the FcRn receptor. Preferred embodiments of said molecules are non-specific IgG and the Fc fragment of IgG (column 3, lines 26-50). Blumberg et al disclose that it is preferred that the antigen is covalently coupled to the FcRn binding partner. Blumberg et al disclose antigens which are characteristic of viruses (column 6, lines 20-34). Blumberg et al also disclose pharmaceutical preparations comprising said compositions with adjuvants, wherein the adjuvants may themselves be covalently coupled to a FcRn binding partner (column 4, lines 9-14), thus fulfilling the specific embodiments of clause (b). Blumberg et al disclose that a variety of administration routes are available depending on the particular conjugate selected, the particular condition being treated and the dosage required for therapeutic efficacy (column 9, lines 58-65).

12. Claim 46 is rejected under 35 U.S.C. 102(e) as being anticipated by Ward (U.S. 6,277,375). The specific limitations of claim 46 are recited above.

Ward discloses a method for increasing the serum half-life of a therapeutic agent comprising conjugating said therapeutic agent to an agent having an increased serum half-life relative to the serum half-life of IgG (column 13, lines 40-45). Ward discloses that agents having a mutant Fc-hinge domain have dramatically increased in vivo half-life in comparison to native Fc-hinge domain (column 10, lines 8-10). Ward discloses the administration of vaccines comprising Fc-hinge domains and therapeutic agents such that fewer "booster vaccinations" are required (column 4, lines 5-8 and column 17, lines 18-22) thus fulfilling the specific embodiment of claim 46, with regard to the antigen of the fusion protein eliciting a stronger immune response than the antigen alone. Ward discloses that the vaccines may comprise adjuvants for enhancing the effectiveness of said vaccine (column 29, lines 8-11 and column 29, line 63 to column 30, line 10). Ward discloses that the vaccine may be administered subcutaneously or intramuscularly (column 29, lines 12-14). Ward discloses that the mutant Fc-hinge region results in increased serum half-life, fulfilling the specific embodiment of a localizing protein, wherein said localizing protein causes and increase in concentration of the antigen. Ward discloses that recombinant vectors encoding Il-2 linked to the mutant Fc-hinge or Fc domain (column 7, lines 22-35).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ward (U.S. 6,277,375) in view of Blumberg (U.S. 6,086,875, reference A7 of the IDS filed October 10, 2001).

Claim 44 is drawn to a method for enhancing the immunogenicity of an antigen in a mammal the method comprising administering to a mammal intramuscularly, intravenously, transdermally or subcutaneously, a first fusion protein comprising an antigen protein with a localizing protein, and a second fusion protein comprising an adjuvant protein with a localizing proteins, said localizing protein causing an increase in concentration of said antigen and adjuvant proteins in a region of the mammal accessible to the immune system. Claim 45 is drawn to a method for enhancing the immunogenicity of an antigen in a mammal the method comprising administering to a mammal intramuscularly, intravenously, transdermally or subcutaneously, a fusion protein comprising an antigen protein, an adjuvant protein and a localizing proteins, said localizing protein causing an increase in concentration of said antigen and adjuvant proteins in a region of the mammal accessible to the immune system.

Ward teaches a method for increasing the serum half-life of a therapeutic agent comprising conjugating said therapeutic agent to an agent having an increased serum half-life relative to the serum half-life of IgG (column 13, lines 40-45). Ward teaches that agents having a mutant Fc-hinge domain have dramatically increased in vivo half-life in comparison to native Fc-hinge domain (column 10, lines 8-10). Ward teaches the administration of vaccines comprising Fc-hinge domains and therapeutic agents such that fewer "booster vaccinations" are required (column 4, lines 5-8 and column 17, lines 18-22) thus fulfilling the specific embodiment of claim 46, with regard to the antigen of the fusion protein eliciting a stronger immune response than the

antigen alone. Ward teaches that the vaccines may comprise adjuvants for enhancing the effectiveness of said vaccine (column 29, lines 8-11 and column 29, line 63 to column 30, line 10). Ward teaches that the vaccine may be administered subcutaneously or intramuscularly (column 29, lines 12-14). Ward teaches that the mutant Fc-hinge region results in increased serum half-life, fulfilling the specific embodiment of a localizing protein, wherein said localizing protein causes and increase in concentration of the antigen. Ward teaches that recombinant vectors encoding Il-2 linked to the mutant Fc-hinge or Fc domain (column 7, lines 22-35). Ward does not teach the administration of two fusion proteins comprising a first protein of antigen linked to that mutant Fc domain and a second protein of adjuvant linked to the mutant Fc domain, not does Ward teach a fusion protein comprising an antigen, adjuvant and the mutant Fc domain.

Blumberg et al teach the cytokines as immunopotentiating agents which include Il-2, and the linking of said cytokines to the Fc fragment of IgG (column 8, line 65 to column 9, line 24 and column 7, lines 38-59).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer Il-2 either as a fusion protein with the antigen and the mutant Fc-domain, or as a separate fusion protein with the mutant Fc domain. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Blumberg on the efficacy of Il-2 as immune potentiating agents and the teachings of Blumberg on the administration of fusion proteins comprising Il-2 and the Fc domain, as well as by the teachings of Ward on fusion proteins comprising Il-2 and the mutant Fc domain, wherein said fusion protein increases the half life of the Il-2 in serum, thus prolonging the therapeutic effect of Il-2.

15. Claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24-25, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falkenberg et al (U.S. 6,406,689) in view of Cardy et al (WO 95/31483). Claim 1 is drawn to a method of enhancing the immunogenicity of an antigen in a

mammal comprising administering to the mammal intramuscularly, intravenously, transdermally or subcutaneously, a fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to the antigen thereby to elicit an immune response against the antigen, wherein the antigen is selected from the group consisting of a prostate-specific membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor specific protein and the antigen of the fusion protein elicit a stronger immune response in the mammal than the antigen alone. Claim 2 embodies the method of claim 1, further comprising administering the fusion protein in combination with an adjuvant in an amount sufficient to enhance the immune response against the antigen of the fusion protein relative to the immune response against the antigen of the fusion protein administered without adjuvant. Claim 3 embodies the method of claim 2 wherein the fusion protein and adjuvant are administered simultaneously. Claim 5 embodies the method of claim 4 wherein the immunoglobulin heavy chain domain comprises an immunoglobulin hinge region. Claim 6 embodies the method of claim 5 wherein the immunoglobulin heavy chain region comprises a region selected from the group consisting of CH2, CH3 and CH4. Claim 7 embodies the method of claim 5 wherein the heavy chain constant region comprises CH2 and CH3. Claim 10 embodies the method of claim 1 wherein the antigen selected from the group consisting of a prostate-specific membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor specific protein. Claim 14 specifies that the mammal in claim 1 is a human.

Claim 15 is drawn in part to a composition for eliciting an immune response against an antigen in a mammal, the composition comprising an admixture for intramuscular, intravenous, transdermal or subcutaneous administration comprising (a) an antigen fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to the antigen admixed with an adjuvant wherein the antigen is selected from the group consisting of prostate-membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor-specific protein. Claim 18 embodies the composition of claim 15 , wherein the immunoglobulin heavy chain region comprises an immunoglobulin hinge region. Claim 19 embodies the composition of

claim 18, wherein the immunoglobulin heavy chain region comprises a region selected from the group consisting of CH2, CH3 and CH4. Claim 20 embodies the composition of claim 18 wherein the heavy chain constant region comprises CH2 and CH3. Claim 22 embodies the composition of claim 15 wherein the antigen is selected from the group consisting of a prostate-specific membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor specific protein. Claim 24 embodies the composition of claim 15 wherein the adjuvant of clause (a) is a cytokine. Claim 25 specifies that the cytokine of claim 24 is a human cytokine. The specific embodiments of claim 46 is recited in section 10 above.

Falkenberg et al teach a method of enhancing the immunogenicity of an antigen in a mammal comprising administering to said mammal intramuscularly, or subcutaneously a dose of inactivated tumor cells or tumor cell portions (column 20, under the heading "The Tumor Cells and Tumor Cell Portions") and a dose of recombinant Il-2 as an adjuvant (column 21, under the heading "Immunostimulants" especially column 22, lines 49-53, column 17, lines 16-19 and column 5, lines 38-40), wherein the Il-2 or the Il-2 and the inactivated tumor cell or portion thereof is contained in a depot formulation (column 23, lines 31-35, see also column 18, lines 4-6 on routes of administration). Falkenberg et al teach that adjuvant can be administered prior to, simultaneous with, or following the administration of an antigen (column 3, lines 44-45). Falkenberg et al teach recombinant human Il-2 as a preferred embodiment of the invention (column 17, lines 16-19). Falkenberg et al do not teach the fusion of a tumor associated antigen with an immunoglobulin Fc domain or the fusion of a cytokine to the immunoglobulin Fc domain.

Cardy et al teach a method for modulating the immune response in a mammal comprising the administration of a chimeric polypeptide comprising a fusion of one or more immunodominant peptides, typically a T-cell epitope, (page 3, lines 10-19), into an immunoglobulin molecule (abstract) having CH2 and CH3 domains as well as a hinge region. Cardy et al teach that the administration of exogenously added peptides in vaccines will normally be taken up and presented only in association with MHC class II, but that the presentation antigens in association with MHC

class I is essential for eliciting a CTL response. Cardy et al teach that the antibody can be targeted to specific antigen-presenting cells in order to better control the type of immune response to the immunodominant peptide(s) and thus result in the presentation of antigens in association with MHC class I (page 4, last sentence, page 5, lines 5-9 and bridging sentence to page 6). Cardy et al specifically teach CTL inducing peptides from MAGE1-3 (page 13, example 3 and page 14, example 5) as well as immunodominant peptides from a viral protein (page 15, example 7).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the chimeric molecule as taught by Cardy et al for the tumor cell portions in the method of Falkenberg et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Cardy et al on the necessity of presenting peptides in association with MHC class I for eliciting CTL activity.

16. Claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24-25, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falkenberg et al (U.S. 6,406,689) in view of Cardy et al (WO 95/31483) and Israeli et al (U.S. 5,538,866). The combination of Falkenberg et al and Cardy et al meet the specific limitations of claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24-25 and 46 for the reasons set forth in section 15, above. It is noted that claims 1, 10 and 15 contain the specific embodiment of a fusion protein comprising a prostate-specific membrane antigen. Falkenberg et al teach antigenic material selected from portions of prostate carcinoma cells (column 20, line 65 to column 21, line 4). Falkenberg et al do not specifically teach prostate specific membrane antigen as a tumor cell portion.

Israeli et al teach prostate-specific membrane antigen as a protein which is highly expressed in prostate cancer tissues including metastatic tissues (column 3, lines 8-11). Israeli et al teach epitopes of PSM antigen which are accessible to antibody binding (column 12, lines 64-67).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute a the chimeric molecule comprising the epitopes of prostate specific membrane antigen as taught by Israeli into the chimeric molecule as taught by Cardy et al as a substitute for the tumor cell portions in the method of Falkenberg et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Cardy et al on the necessity of presenting peptides in association with MHC class I for eliciting CTL activity and the teachings of Israeli et al on the over expression of prostate-specific membrane antigen in primary and metastatic prostate cancer cells.

17. Claims 1-3, 5-7, 10, 14, 15, 18-22, 24-25, and 46 and rejected under 35 U.S.C. 103(a) as being unpatentable over Falkenberg et al (U.S. 6,406,689) and Cardy et al (WO 95/31483) as applied to claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24-25, and 46 in section 15, above, and further in view of Liu et al (Blood, 1998, vol. 92, pp. 3730-3736) and Roitt et al (Immunology (text), 1993, page 8.4). Claim 21 is drawn to the composition of claim 15 wherein the adjuvant of clause (a) comprises an oligonucleotide CpG sequence. The combination of Falkenberg et al (U.S. 6,406,689) and Cardy et al (WO 95/31483) render obvious the limitations of claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24-25, and 46 for the reasons set forth in section 15 above. Cardy et al teach the targeting of antigens to antigen-presenting cells such as macrophage by means of the Fcgammal receptor (page 5, bridging sentence to page 6). Neither reference teaches and oligonucleotide CpG sequence as an adjuvant.

Liu et al (Blood, 1998 vol. 92, pp. 3730-3736) teach that oligonucleotide CpG sequences can induce the activation of B cells and antigen presenting cells such a macrophage and monocytes (page 3730, first column, lines 11-13). Liu et al teach that mice immunized with tumor antigen and CpG ODN as an adjuvant were protected from tumor challenge at the same level as mice immunized with tumor antigen and the well known Freund's adjuvant (page 3730, first column, bridging sentence to column 2). Liu et al teach that CpG was more effective than

Freund's Adjuvant at producing a IgG2a anti-Id response thus suggesting a TH1 response (page 3730, second column, last sentence of the first full paragraph).

Roitt et al teach that a TH1. response activates macrophage and sensitizes TH1 helper cells to antigen presenting macrophage (page 8.4, first paragraph).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use an oligonucleotide CpG sequence for an adjuvant to the composition of claim 15. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Liu et al on the level of protection against tumor cells afforded by CpG as an adjuvant, and the evidence that CpG elicited an IgG2a anti-id response consistent with a TH1 response. One of skill in the art would be motivated to induce a TH1 response as a TH1 cells activate macrophage and are more sensitive to antigen presented from said activated macrophage. One of skill in the art would conclude that combining of antigen targeting to macrophage with increased sensitivity to antigen presented by said targeted CpG activated macrophage would further enhance the immunogenicity of the antigen.

18. Claims 1-7, 10-20, 22, 24, 25 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Falkenberg et al and Cardy et al as applied to claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24, 25, and 46 above, and further in view of Aruffo et al (U.S. 5,709,859) and Ward (U.S. 6,277,375).

Claim 4 embodies the method of claim 1 wherein the adjuvant comprises a fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to an adjuvant protein. Claim 8 embodies the method of claims 1 or 4 wherein the immunoglobulin heavy chain constant region has the same amino acid sequence as the immunoglobulin heavy chain constant region of the mammal. Claim 9 embodies the method of claim 8 wherein the amino acid sequence is a human immunoglobulin heavy chain constant region. Claim 11 embodies the method of claim 4 wherein the adjuvant protein is a cytokine, claim 12 specifies that the cytokine

of claim 11 is defined by an amino acid sequence corresponding to an amino acid sequence defining a cytokine present in the same species as the mammal. Claim 13 specifies that said cytokine is a human cytokine. Claim 15 embodies the limitation as recited above, in section 11, wherein the composition comprises an antigen fusion protein of clause (b) wherein the antigen is selected from the group consisting of prostate-membrane antigen, an ectodomain of a cytokine receptor, a viral protein and a tumor-specific protein, admixed with an adjuvant fusion protein comprising an immunoglobulin heavy chain constant region linked by a polypeptide bond to an adjuvant protein. Claim 16 embodies the composition of claim 15 wherein the adjuvant of clause (a) comprises a fusion protein comprising an immunoglobulin constant region linked by a polypeptide bond to an adjuvant protein. Claim 17 embodies the composition of claim 15 wherein the antigen of clause (b) is linked by a polypeptide bond to an immunoglobulin heavy chain constant region. Claim 26 embodies the composition of claims 15 or 16 wherein the immunoglobulin heavy chain constant region is a human heavy chain constant region.

The specific limitations of claims 44 and 45 are set forth in section 14 above.

The combination of Falkenberg et al and Cardy et al renders obvious claims 1-3, 5-7, 10, 14, 15, 18-20, 22, 24, 25, and 46 for the reasons set forth in section 15 above. It is noted that because Cardy et al teach the targeting of specific antigen presenting cells such as macrophage and B cells, he specific limitation of claims 44 and 45 with respect to "localizing proteins" are fulfilled as antibodies which bound to the FcRI receptor or the B-cell receptor would act as a localizing protein to said cells. However, neither Falkenberg nor Cardy et al teach a method or composition wherein a cytokine is fused to an immunoglobulin heavy chain region by means o a peptide bond. Further, neither Falkenberg et al nor Cardy specifically teach that the Fc domain is a human Fc domain.

Ward teaches the production of recombinant Il-2 molecules fused by a peptide linkage to a mutant Fc or Fc-hinge domain for increasing the serum half like of Il-2 (column 7, lines 22-34).

Ward teaches recombinant human Fc domain and Fc-hinge domain fusion proteins (column 18, lines 26-38).

Aruffo et al teach fusion proteins comprising extracellular domains of endothelial and granulocyte surface receptors responsible for neutrophil-endothelium binding fused to a human IgG constant region (column 8, lines 54-60). Aruffo et al teach that human proteins are less immunogenic than non-human monoclonal antibodies.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer Il-2 as a separate fusion protein comprising a Fc domain of an immunoglobulin molecule or to administer Il-2 as part of a fusion protei comprising the antigen and the Fc domain of the immunoglobulin molecule. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Falkenberg et al on the administration of Il-2 as an adjuvant for tumor cells; the teachings of Ward on the increase in serum half life afforded by the conjugation of Il-2 to the Fc domain; and the teachings of Aruffo et al on the decreased immunogenicity afforded by the administration of human proteins to human subjects. One of skill in the art would be motivated to maintain a longer serum half life in order to decrease the amount of recombinant human Il-2 used in the method. Further, one of skill in the art would use a humanized antibody carrying immunodominant tumor associated antigen or antigens in the method taught by Cardy et al, as one of skill in the art would be motivated to limit the immune response to the immunodominant tumor associated antigen as opposed to the immunodominant tumor associated antigen and the Fc domain in order to avoid unnecessary side effects from an increased immune response directed toward the immunoglobulin constant region which would not provide any therapeutic efficacy in the treatment of cancer or viral diseases.

19. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Laus et al (U.S. 6,080,409, reference A6 of the IDS submitted October 10, 2001) in view of what is suggested in the reference.

Claim 45 is drawn to a method for enhancing the immunogenicity of an antigen in a mammal the method comprising administering to a mammal intramuscularly, intravenously, transdermally or subcutaneously, a fusion protein comprising an antigen protein, an adjuvant protein and a localizing proteins, said localizing protein causing an increase in concentration of said antigen and adjuvant proteins in a region of the mammal accessible to the immune system.

Laus et al teach a method of enhancing the immunogenicity of a tumor associated antigen in a mammal comprising the administration of a fusion protein comprising the tumor associated antigen and a dendritic cell binding protein (column 11, lines 10-13 and column 5, lines 28-31)). Laus et al teach that dendritic cell binding proteins such as GM-CSF activate dendritic cells and that the administration of said fusion proteins results in a T-cell response that is much higher than that stimulated by the antigen alone (column 3, lines 20-48). Laus et al also teach that viral antigens as opposed to tumor associated antigens are also within the scope of the invention (column 4, lines 7-16). Laus et al teach that mature dendritic cells in the peripheral blood are the most potent antigen presenting cells. Laus et al teach that fusion proteins comprising antigen and dendritic cell binding proteins enables mature dendritic cells to take up the antigen (column 9, lines 20-32 and lines 44-46). Because the dendritic cell binding proteins also activate the dendritic cells and result in an enhanced immune response, the binding proteins are both adjuvants and localizing proteins. Thus the fusion proteins of Laus et al fulfill the specific embodiment of claim 45 with respect tot e fusion protein comprising an adjuvant protein and a localizing protein, as in the case of the dendritic cell binding proteins they are the same. Laus et al do not specifically teach the route of vaccination with said fusion proteins, although Laus et al teach that dendritic cells activated ex vivo are injected intravenously(column 10, lines 54-57).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the fusion proteins comprising tumor associated or viral antigens fused to dendritic cell binding proteins wherein the route of administration in intravenous. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Laus et al on the ability of GM-CSF to stimulate mature dendritic cells in the blood to take up antigen. One of skill in the art would be motivated to administer the fusion proteins comprising antigens and dendritic cell binding proteins to dendritic cells in the blood and thus would use intravenous injection as an obvious method route of administration.

Conclusion

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

March 18, 2003